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Characteristics of Topics in Pharmacovigilance in The Netherlands†

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† This article is dedicated to the memory of Dr Cees P.H. van Dijke.

Summary

A retrospective analysis was made of the nature and composition of 107 consecutive topics presented in publications by or in collaboration with the national pharmacovigilance centre in The Netherlands, containing data obtained through 'spontaneous reporting'. These topics were published in various national and international professional journals or special bulletins or as 'dear doctor letters'. The topics constituted a wide variety of events and disorders. There was, however, a predominance of concrete, characteristic and often serious diseases, notably specific hypersensitivity reactions (43%, e.g. anaphylaxis, blood dyscrasias and liver injury), toxic manifestations or syndromes (30%, especially involving the nervous system), and drug interactions (13%). Most topics presented predominantly qualitative information. 62% of topics concerned type B, 33% type A and 3% type C adverse drug effects. The topics often referred to small numbers of case reports: 10 or less in 70% of the 107 topics. 46% of the topics concerned new information. There was some predominance of established (56%) over new drugs. Five pharmacotherapeutic groups accounted for 74% of topics. Of the 72 approved drugs or drug groups, 12 (17%) have been removed from the market. These findings increase our understanding of the functioning of pharmacovigilance and may enable further improvement of the methods and strategies involved.

Spontaneous reporting (i.e. the countrywide reporting system for suspected adverse drug reactions, currently often referred to as pharmacovigilance) was first started in The Netherlands in 1963.[1] The first 10 years of The Netherlands national pharmacovigilance centre (Pharmaceutical Inspection, Ministry of Health) were characterised by experimentation and change. During that period results of the system were only rarely used publicly. The next 18 years (1973 to 1990) were a period of relative stability and consolidation of procedures. During these years, the first author of this paper was director of the centre.

The major aims of pharmacovigilance are the early detection of new adverse effects, identification of risk factors and mechanisms, quantitative risk assessment, and analysis and dissemination of information. Pharmacovigilance is still under development, and improvements may yet be needed.

We retrospectively analysed the nature and composition of the topics addressed during the period 1973 to 1990 in publications by or in collaboration with the pharmacovigilance centre in The Netherlands, containing data from original case reports. The purpose was to find out whether certain characteristics and patterns can be recognised that may be of value for further improvements in pharmacovigilance. The contributions of pharmacovigilance to the drug regulatory authority (the Medicines Evaluation Board), e.g. changes in the product information sheets or withdrawals, were not studied because of the secrecy observed by this Board.

1. Pharmaceutical defects
2. Various types of adverse drug effects and interactions:
2.1 Laboratory findings
2.2 Complaints and symptoms of varying specificity
2.3 Diseases and syndromes (pharmacologically or phenomenologically definitive)
2.4 Drug interactions
3. Drug profiles (review of reported adverse effects)
4. Therapeutic failure
5. Unexpected therapeutic effects

Fig. 1. Topics in pharmacovigilance.

Materials and Methods

Methods

The pharmacovigilance system in The Netherlands is based on countrywide 'spontaneous reporting' by physicians and, less frequently, by pharmacists and dentists of cases of suspected adverse drug effects.[1] All published information that had been issued by or in collaboration with The Netherlands national pharmacovigilance centre was collected during the period 1973 to 1990, e.g. in professional bulletins or journals or as 'dear doctor letters'. These communications were screened for the presence of topics (i.e. information concerning a specific adverse event or other problem in relation to one or more drugs) referring to case reports received through spontaneous reporting, with or without data from other sources.

Drug-related events and problems are extremely varied, ranging from simple complaints or abnormal laboratory values to full-blown and serious diseases. In order to identify characteristics and patterns, the topics were grouped using a classification based on event nature, clinicopathological and pharmacological determinants, and relevance, as shown in figures 1 and 2.

The various drug-induced diseases and syndromes (item 2.3) were subdivided as in figure 2.

1. Immunoallergic hypersensitivity
1.1 Nonspecific reactions (e.g. rashes)
1.2 Specific hypersensitivity (e.g. anaphylaxis, hepatitis, blood dyscrasias)
2. Manifestations of drug toxicity (e.g. organ toxicity, hormonal effects, embryotoxicity)

Fig. 2. Classification of drug-induced diseases and syndromes.

Classification of Adverse Effects

Adverse effects were classified according to established categories: type A, B and C effects.[2-4] Type A effects ('drug actions') are those resulting from exaggerated pharmacological actions or from interactions between drugs. Type A effects tend to be fairly common, dose related, and may be avoided by using doses that are appropriate to the individual patient. Such effects can usually be reproduced and studied experimentally, and are often already identified before marketing.

Type B effects ('patient reactions') characteristically occur only in a minority of patients and include immunoallergic and 'idiosyncratic' reactions, and intolerance due to abnormal metabolism. Type B effects may display little or no dose

relationship, but often there is a suggestive time relationship between drug intake and onset and course. They generally are unpredictable, may be serious, and are notoriously difficult to study experimentally.

Type C effects refer to situations where the use of a drug may (often for unknown reasons) increase the frequency of a 'spontaneous' disease. Type C effects may be both serious and relatively common (and include malignant tumours), and may have pronounced effects on public health. These events may be coincidental and frequently involve long term effects; there often is no suggestive time relationship and the connection may be very difficult to prove.

Classification According to Group and 'Age'

The suspected drugs in the topics were classified according to pharmacotherapeutic group and 'age'. A drug was considered 'new' when the interval between the introduction of the drug (as mentioned in the Informatorium Medicamentorum of the Royal Dutch Society for the Advancement of Pharmacy[5]) and the year of publication of the communication was 6 years or less, and 'established' when the interval was 7 or more years.

The limit of 6 years was chosen because regulations in the European Union require intensified pharmacovigilance for 5 years after the registration of a drug, whereas there may be a delay of about 1 year between the reporting of an adverse drug effect and the publication of the information. For example, the mean delay between the diagnosis of adverse drug reactions and their publication in medical journals was found to be about 63 weeks (for first reports).[6] For drug interactions, the age of only one of the drugs was considered, either that of the acting drug or that of the affected drug.

Assessment of New Adverse Effects

An assessment was made of whether the adverse effects were new or not. A topic was considered 'new' when in the publication no reference was made to relevant information in the data sheet or in the literature (i.e. previously described case histories). When similar cases had been published in the same year, the topic was nevertheless considered new (unless the topic appeared as a reaction to the earlier report). When a topic was addressed for a second time it was no longer considered new. The topics were studied in a quantitative way by counting the numbers of case reports involved.

- Type of adverse effect
- 'Age' of suspected drug
- New topic?
- Number of case reports involved
- Source of case reports (national or international)
- Withdrawal from the market?

Fig. 3. Further pharmacovigilance topics assessment items.

Sources of Reports

With regard to sources of the reports, the topics were divided into 2 groups: referring only to case reports in The Netherlands or to reports in one or more additional countries.

Finally, drugs that have been removed from the market after the topic was published were identified. However, because of the secrecy in drug regulation, the question of whether the adverse effect had caused or contributed to withdrawal could not be addressed. These assessment items are summarised in figure 3.

Results

In the study period (1973 to 1990), a total of 107 topics were presented in a variety of different publications by or in collaboration with the pharmacovigilance centre in The Netherlands. These publications contained information derived from original case reports (tables I to V).

Several publications concerned more than one topic and several topics were addressed in more than one publication. There were 81 articles or letters in national or international professional journals. A special Adverse Reactions Bulletin (Bulletin Bijwerkingen) was produced by the

Table I. Review of 107 pharmacovigilance topics

Topic summary	Suspected drug	Ref[a] no.	ADR type	New topic?	No. of cases	Age of drug[b]
Pharmaceutical defects						
Fragmentation of inhalation capsules	Cromoglycate and salbutamol	1		Yes	4[c]	19/18
Laboratory findings						
Hyperammonaemia (in adults)	Sodium valproate	2	A	Yes	4[c]	11
Complaints and symptoms						
Cough	ACE inhibitors (captopril/enalapril)	3	A	No	21[c]	5/1
Testicular and perineal pain	Mazindol	4,	B	No	8[d]	8
		5	B	No	4[c]	10
Diseases and syndromes						
Immunoallergic hypersensitivity						
Nonspecific reactions (mainly rashes)	Camazepam[e]	6	B	Yes	13[c]	6
	Coumarin derivatives	7	B	No	16[c]	> 20
	Indapamide	8	B	Yes	204[d]	13
	Mebendazole	9	B	Yes	8[c]	14
	Placebo capsules containing quinine (capsulae albochin)	10	B	No	1[c]	> 20
	Terfenadine	11	B	Yes	108[d]	3
	Ticlopidine[e]	12	B	No	1[c]	3
Contact dermatitis	Udder ointment (human use of veterinary product)	13	B	No	2[c]	
Specific hypersensitivity						
Anaphylaxis and acute hypersensitivity	Cinoxacin	14	B	Yes	26[d]	5
	Floctafenine	15	B	No	13[c]	11
	Glafenine[e]	16,	B	No	32[c]	9
		17	B	No	116[c]	12
	Isoflurane	18	B	Yes	1[c]	4
	Ketoconazole	19	B	Yes	2[c]	2
	Mebhydrolin	20	B	Yes	3[c]	> 20
	Paracetamol	21	B	Yes	55[d]	> 20
	Polidocanol	22	B	No	3[c]	> 20
	Promethazine	23	B	Yes	2[c]	> 20
Review of reports of anaphylactic reactions; high reporting rate of glafenine[e]		20	B		229[c]	
Liver						
Hepatitis	Diclofenac	24	B	No	1[c]	10
	Glafenine[e]	25,17	B	No	5[c]	12
	Halothane	26	B	No	1[c]	15
	Ketoconazole	27	B	No	5[c]	2
	Nomifensine	28	B	Yes	7[d]	3
	Phenprocoumon	29	B	No	1[c]	> 20
	Pirprofen	30,31	B	No	4[d]	5
Cholestatic hepatitis	Amoxicillin-clavulanic acid	32,	B	Yes	1[c]	6
		33	B	No	5[d]	7
Hepatitis, serial clinicopathological studies	Flutamide	34	B	Yes	1[c]	0
	Allopurinol	35	B	No	6[d]	> 20
	Glafenine	36,31	B	No	38[c]	19
	Ketoconazole	37,31	B	No	55[c]	5
	Nitrofurantoin/ nifurtoinol	38,31	B	No	52[c]	19/22

Contd

Table I. Continued

Topic summary	Suspected drug	Ref[a] no.	ADR type	New topic?	No. of cases	Age of drug[b]
Blood						
Granulocytopenia	Aprindine	39,40	B	Yes	8[c]	2
	Mianserin	41	B	No	4[c]	4
	Pirenzepine	42	B	Yes	1[c]	3
	Spironolactone	43,44	B	Yes	1[c]	> 20
	Ticlopidine[e]	12	B	No	1[c]	3
Review of agranulocytosis reports; high reporting rate of pyrazolinone derivatives[e]		45,46	B	-	90[c]	
Demonstration of drug-dependent antibodies against hematopoietic precursor cells in agranulocytosis	Propylthiouracil	47	B	Yes	1[c]	> 20
Thrombocytopenia	Mianserin (drug-dependent antibodies)	48,41	B	Yes	1[c]	3
	Nalidixic acid	49,50	B	Yes	6[c]	> 20
	Pirenzepine	42	B	Yes	1[c]	3
	Ticlopidine (drug-dependent antibodies)[e]	12,51	B	Yes	1[c]	3
Other organs and systems						
Fever	Labetolol	52,53	B	Yes	2[c]	8
	Nomifensine	28	B	Yes	22[d]	3
	Pyrazinamide	54	B	No	1[c]	> 20
Pancreatitis	Methyldopa	55	B	No	1[c]	19
Parotitis	Nitrofurantoin	56,57	B	No	2[c]	13
Interstitial nephritis	Cimetidine	58	B	Yes	1[c]	3
	Glafenine[e]	17	B	No	NS[c]	12
Sclerosing peritonitis	Practolol[e]	59,60	B	No	5[c]	4
Photosensitivity	Azapropazone	61,	B	No	5[c]	13
		62	B	No	190[d]	13
Drug toxicity (e.g. organ toxicity, hormonal effects, embryotoxicity)						
Sterile meningitis	Metrizamide[e]	63	B	Yes	NS[c]	4
Optic neuropathy	Amiodarone	64	B	Yes	13[d]	18
	Ethambutol/ isoniazid	65	B	No	2[c]	> 20
Psychiatric complications (depression, anxiety, mania, depersonalisation; withdrawal reactions)	Fenfluramine	66	A	No	13[c]	> 20
Peculiar visual and psychic disturbances	Benzydamine[e]	67	A	Yes	10[c]	6
Hallucinations in children	Oxolamine[e]	68,	A	Yes	4[c]	12
		69	A	No	20[d]	15
Acute extrapyramidal dystonic reactions	Domperidone	70,	A	No	9[c]	9
		71	A	No	11[d]	10
Psychic agitation	Budesonide	72	B	Yes	2[c]	5
Depression and dyskinesia	Flunarizine	73,	C	Yes	8[c]	3
		74	C	No	22[c]	3
Psychosis, amnesia, behavioural disturbances	Triazolam[e]	75,	B	Yes	> 100[c]	1
		76	B	No	1000[c]	11
Paradoxical motion sickness-like syndrome after withdrawal	Scopolamine TTS	77,78	B	Yes	3[c]	1
Prolonged postoperative apnoea	Ketamine	79	A	Yes	1[c]	15
Apnoea after epidural administration	Sufentanil	80	A	No	4[c]	New
Sudden unexpected death in asthma patients	β_2-sympathomimetic aerosols	81	C	No	26[c]	ca 14
Body temperature elevation	Oral contraceptives	82	A	Yes	1[c]	> 20
Gynaecomastia	Captopril	83	B	Yes	1[c]	7
Interruption of menstruation	Naproxen	84	A	Yes	2[c]	6

Contd

Table I. Continued

Topic summary	Suspected drug	Ref[a]	ADR type	New topic?	No. of cases	Age of drug[b]
Acute renal failure	Fumaric acid-esters	86,87	A	No	4[c]	Old
Oesophageal ulcers	Doxycycline/ tetracycline capsules	88	A	No	1[c]	> 20
Hyperthyroidism	Kelp (*Fucus vesiculosis*)	85	A	No	1[c]	
	Doxycycline tablets	89	A	Yes	2[c]	16
	Pinaverium bromide	90	A	No	5[c]	2
Review of reports of oesophagus injury		91	A		57[c]	
Nicolau syndrome (muscle and skin necrosis)	Pyrazolinone derivatives[e]	92	B	No	3[c]	> 20
Biliary concrements and colic	Ceftriaxone	93,94	A	Yes	2[c]	5
Phlebitis	Ergotamine	95	A	No	7[c]	> 20
Face malformations	Coumarin derivatives	96,97	A	No	3[c]	> 20
Spina bifida	Sodium valproate	98	A	No	10[c]	13
Drug interactions						
Potentiation of coumarins	Amiodarone	99,100	A	No	7[c]	12[f]
	Azapropazone	101,102	A	Yes	NS[c]	1[f]
	Flurbiprofen	103,104	A	Yes	2[c]	2[f]
	Oxolamine[e]	105	A	Yes	2[c]	5[f]
	Cotrimoxazole	106	A	No	3[c]	6[f]
Inhibition of coumarins	Acetylcysteine	107	A	Yes	1[c]	1[f]
	Colestyramine	108	A	No	5[c]	2[f]
	Unexpected enzyme induction caused by barbiturates in obsolete hypnotics, e.g. Bellanox[e]	109	A	No	4[c]	18[f]
	Modifast	110	A	Yes	NS[c]	2[f]
Inhibition of oral contraceptives	Anticonvulsants	111	A	Yes	3[c]	12[g]
	Griseofulvin	112	A	Yes	22[d]	> 20[g]
	Minocycline	113	A	Yes	1[c]	17
Alcohol intolerance	Ketoconazole	114	B	No	1[c]	8[f]
Potentiation of amantadine	Hydrochlorothiazide/ amiloride	115	A	No	1[c]	8[g]
Drug profile	Nitrofurantoin	116			218[c]	13
Review of reported suspected adverse effects; no increase in reporting						
Therapeutic failure						
Insufficient analgesia and decreased efficacy of subsequent morphine in cancer patients	Buprenorphine (sublingual)	117		Yes	2[c]	New

a References to the publications in this table are published in the appendix.
b Age of drug = year of publication of communication minus year of introduction, as mentioned in the Informatorium Medicamentorum of the Royal Dutch Society for the Advancement of Pharmacy.
c Dutch case reports only.
d Case reports from 2 or more countries.
e Withdrawn from the market.
f Age of acting drug.
g Age of affected drug.
Abbreviations: ADR = adverse drug reaction; NS = not specified.

pharmacovigilance centre in 3 volumes (1985 to 1987), and was distributed to all doctors and pharmacists in the country. Two articles were published in the Drugs Bulletin (Geneesmiddelenbulletin) issued by the Ministry of Health. Three letters were sent directly to medical practitioners and pharmacists ('dear doctor letters'). 12 topics were presented in *Tromnibus*, a periodical issued by the Federation of Dutch Thrombosis Services.

In our survey, duplicate publications of topics referring to the same case reports (e.g. in a foreign language) were not counted separately, although

the references are added to table I. (A few identical and simultaneous publications in a second journal were not included.) Topics that were addressed for a second time and contained additional information (e.g. follow-up reports or international studies), on the other hand, were regarded as separate topics.

Table II. Characteristics of 107 pharmacovigilance topics

	No. of topics	%
No. of case reports		
1	27	25
2-10	48	45
11-50	15	14
51-100	5	5
> 100	8	7
Not specified	4	4
Source of case reports		
Netherlands only	92	86
Netherlands and one or more other countries	15	14
Type of adverse effects		
Type A effects	35	33
Type B effects	66	62
Type C effects	3	3
Not applicable	3	3
New or established drugs?		
New drug[a]	42	39
Established drug[b]	60	56
Not applicable	5	5
New topic?		
Yes	49	46
No	54	51
Not applicable	4	4

a Registered 6 or less years before publication of topic.
b Registered 7 or more years before publication of topic.

Table III. Unapproved drugs in 6 topics

Fumaric acid esters (used in psoriasis)
Capsulae albochin Formularium Nederlandse Apothekers (FNA), placebo capsules containing quinine for bitter taste
Kelpasan, a kelp (*Fucus vesiculosis*) product containing iodine
Modifast, a slimming product containing vitamin K and sold only in pharmacies
Sufentanil for epidural anaesthesia (at that time not yet approved)
Veterinary udder ointment containing phenoles and citronellal used for self-medication in humans

Table IV. Withdrawn drugs

Hypnotics containing barbiturates (e.g. secobarbital/brallobarbital/amobarbital in Bellanox)
Benzydamine (oral use)
Camazepam
Glafenine
Metrizamide
Nomifensine
Oxolamine
Pirprofen
Practolol
Pyrazolinone derivatives (e.g. Baralgin, Buscopan comp, Butazolidine, Irgapyrine, Tanderil, Tomanol)
Ticlopidine
Triazolam[a]

a Triazolam was withdrawn in 1979 and reintroduced in 1990.

Table V. Pharmacotherapeutic drug categories in 107 pharmacovigilance topics (more than one category per topic possible)

Category	No. of topics	%
Drugs acting on the central nervous system	22	18
Anti-infective agents	20	17
Analgesic and antirheumatic drugs	19	16
Anticoagulants	16	13
Cardiovascular drugs	12	10
Other	32	26

The 107 topics are reviewed in table I, specifying the nature of the adverse events (in summary), suspected drugs, references to the publications, types of adverse effects, numbers of case reports, 'age' of the drugs, and whether or not the topics were new. 66 (62%) topics were classified as type B effects and 35 (33%) as type A effects, including 13 of the 14 drug interactions. Three topics concerned type C effects (3%). Three topics did not refer to an adverse effect, but to a pharmaceutical defect, a therapeutic failure and a drug review, respectively.

Seventy-five (70%) of the 107 topics referred to 10 or less case reports, including single cases in 27 topics (table II). In 15 (14%) topics the number of case reports was between 11 and 50, whereas in

13 (12%) topics more than 50 case reports were involved. In 4 topics the numbers of cases were not precisely specified. 42 (39%) topics concerned new medicines, whereas 60 (57%) referred to established products. 49 (46%) topics were considered new; 54 (51%) had been described previously. In the reviews of anaphylactic reactions, agranulocytosis and oesophageal injury, the question of whether drug and topic were new was not addressed; in the review of nitrofurantoin, the latter question only was thought not to be relevant. Furthermore, for 2 unapproved drugs the age question was considered inappropriate.

In 92 (86%) topics the data were limited to Dutch case histories; 15 (14%) case reports from one or more other countries were also included. The reviews of anaphylactic reactions, agranulocytosis and oesophageal injury referred to many different drugs and are not included in this figure. 72 different approved drugs or drug groups and 6 unofficial drugs were involved in the topics (tables I and III). Of the 72 approved drugs, 12 (17%) have been withdrawn from the market (table IV). The 5 pharmacotherapeutic drug groups most frequently involved are listed in table V.

Discussion

From the start, the use of data reported to The Netherlands pharmacovigilance centre in publications has been limited by confidentiality and uncertainty with regard to the role of the suspected drugs. During the study period there was, however, an obvious tendency to use the data to their best advantage in publications for the medical/pharmaceutical community. The choice of the topics was influenced by the interests and concerns of the pharmacovigilance centre and its Advisory Committee. Case reports may attract attention for several reasons, e.g. because the drug is new, the adverse event is unexpected, serious or little known, or because of the scientific value of the data. In other cases a request for information from outside (e.g. someone preparing an article) may lead to the inclusion of case reports in a publication.

There were different types of publications: warning letters, brief communications, original journal articles, or additions to articles by others.

As table I shows, there was a remarkable pluriformity of topics encountered in pharmacovigilance in The Netherlands, illustrating the diversity and heterogeneity of adverse drug effects. At the same time, however, there appeared to be a predominance of concrete, characteristic and often serious diseases, notably specific hypersensitivity reactions (n = 46; 43%), e.g. anaphylaxis (n = 11; 10%), blood dyscrasias (n = 11; 10%) and liver injury (n = 14; 13%), toxic manifestations or syndromes (n = 32; 30%) – especially involving the nervous system (n = 17; 16%), and drug interactions (n = 14; 13%); altogether 86% of topics. This pattern resembles that in the study of drug withdrawals by Spriet-Pourra and Auriche.[7] In that study, of 66 products withdrawn because of clinical adverse effects, 14 (21%) were associated with liver injury, 12 (18%) with blood dyscrasias, and 9 (14%) with neurological disorders, together accounting for 33 (50%) withdrawals.

The majority of topics (62%) concerned type B adverse effects. This is likely to reflect the situation that type B effects are a primary concern of pharmacovigilance in the first place. However, type A adverse effects occur with relatively high frequency and in great variety, and this finding also suggests that spontaneous reporting is especially effective in detecting type B effects. Of the 35 topics classified as type A effects, 13 were drug interactions. The 9 interactions with coumarin derivatives were reported with the aid of a reporting project in collaboration with the countrywide organisation of 69 regional outpatient anticoagulant monitoring centres (Dutch Federation of Thrombosis Services).[8]

Only 3 topics were considered to relate to type C effects. Depression and parkinsonism in association with flunarizine were categorised as type C effects because of the possibility of coincidence (2 different publications). The inquiry on sudden and unexpected death during the use of β_2-sympathomimetic aerosols (the other type C effect) was

performed after receiving a few spontaneous case reports. The results confirmed the existence of the association, but a cause-effect relationship remained uncertain.

In the light of the historical thalidomide tragedy, it is worth mentioning that 2 topics (2%) concerned congenital malformations (coumarins and valproic acid). Mebhydrolin-induced anaphylaxis, one of the many associations in the review of anaphylactic reactions, was included as a separate topic because it had not been published previously. For one drug (nitrofurantoin), a profile of the reported suspected adverse effects was included in a review article.

One single topic referred to a pharmaceutical defect, i.e. fragmentation during administration of capsules containing powder for inhalation (cromoglycate or salbutamol). Therapeutic failure was reported only once (buprenorphine in cancer patients), but it should be added that in the 7 topics on inhibition of oral contraceptives or coumarins, lack of effect was of course the major issue. There were no unexpected therapeutic effects.

With regard to suspected drug involvement, it is noteworthy that there was a predominance of established (56%) over new drugs (39%) ['not appropriate' in 5%]. Of the 49 topics classified as new, 20 (41%) concerned established drugs. These findings emphasise that pharmacovigilance should not be restricted to new medicines only. It also shows the relativity of the rule recently introduced in the European Union, that 5 years after registration of a medicine pharmacovigilance is considerably relaxed.

Less than half of the topics (46%) were considered new. Many more topics, however, had an obvious news value, e.g. because the adverse effects were only recently detected or were little known in the medical community. Original observations concerning adverse effects that have only once or twice been reported in the distant past may be of considerable value. In addition, the various review articles and clinicopathological studies, although not classified as new topics, presented many new pieces of information.

An interesting finding was that many of the pharmacovigilance topics referred to fairly small numbers of case reports (table II). In 70% of the topics, 10 or fewer case reports were involved. In the 49 topics classified as new, a similar pattern was found: in 37 (76%) the number of case reports was 10 or fewer. This is in accordance with a recent study in the UK. Of 46 problems naming one drug and one serious (type of) reaction, published in *Current Problems*, 24 (52%) were concerned with 10 or fewer yellow card reports, and of these 12 (26%) with only 4 or fewer cases.[9] These findings are in keeping with the view of the WHO Collaborating Centre for International Drug Monitoring that in the signalling of type B adverse effects, a minimum of some 3 to 9 case reports is often needed.[10,11]

The situation that there is a minimal number of reports needed to provide sufficient evidence for the detection of an adverse effect suggests that the time needed for detection is directly dependent upon the rate of reporting. The smaller the proportion of doctors reporting, the smaller the monitored population of drug users, and the longer it takes before the required minimal number of adverse reaction patients have accumulated.

In 13 topics, on the other hand, more than 50 case reports were involved. Two of these were serial studies of clinicopathological patterns: hepatic injury with ketoconazole and nitrofurantoin, respectively. Only in these 2 studies was an estimation of the frequency of the adverse effect made. For 5 other drugs the numbers of reports were thought to reflect relatively frequent adverse reactions, without further specification, i.e. azapropazone (photosensitivity), glafenine (anaphylactic reactions), indapamide (rashes), pyrazolinone derivatives (agranulocytosis), and triazolam (psychic disturbances).

Triazolam (which received an unusually large number of reports in 1979), was a special case that has been reviewed in detail elsewhere.[12]

In the review article on nitrofurantoin it was concluded that there were no indications for an increase in reporting, relative to the consumption of

the drug. Four of the topics referring to more than 50 case reports were cumulative international studies (i.e. on azapropazone, indapamide, paracetamol and terfenadine).

Five pharmacotherapeutic groups accounted for a total of 74% of the topics: drugs acting on the central nervous system, anti-infective agents, analgesic and antirheumatic drugs, anticoagulants, and cardiovascular drugs (table V). Many of these drugs are known causes of relatively frequent and/or serious adverse effects. The emergence of anticoagulants to some extent reflects the above-mentioned special interaction reporting project. The absence of cytotoxic drugs, on the other hand, undoubtedly reflects selective under-reporting.

The majority of topics (n = 101; 94%) concerned approved drugs. In addition, 2 topics concerned unapproved remedies, one topic concerned the human use of a veterinary product, one involved a warning for the presence of quinine in a placebo (capsulae albochin), one concerned the unapproved use of a registered drug, and one referred to a pharmacy-only slimming product interacting with coumarin anticoagulants (table III).

Clinical Implications

Pharmacovigilance is a complex process of data collection, assessment and distribution, aiming at the safe use of medicines and the prevention of adverse effects. A better understanding of the mechanisms and procedures involved and their scientific, logistic and educational aspects may enable further improvements. The experiences with pharmacovigilance in The Netherlands lend support to the following observations:

1. Pharmacovigilance must continuously hold an open mind for the new, the unusual and the unexpected. The routines involved should enable the precise recording of case histories and not lead to simplification or distortion of adverse events.

2. Spontaneous reporting is particularly useful in the detection of type B adverse effects and of type A effects that were not identified during clinical testing (including drug interactions), but is of less value in the study of type C effects.

3. A limited number of adverse effects are responsible for the majority of the more serious problems encountered in pharmacovigilance. Pharmacovigilance may be improved by intensified monitoring of these effects.

4. Information derived from only small numbers of case reports may already provide valuable information and lead to the detection of new adverse effects.

5. The provision of first reports (i.e. on new adverse effects) is a major role of pharmacovigilance.

6. In addition, the dissemination to healthcare practitioners of all sorts of information relevant to the knowledge of adverse effects and the appropriate use of medicines (including reminders of previously reported adverse effects) is an important function of pharmacovigilance.

7. Pharmacovigilance should cover all drugs on the market, new and established, approved and nonorthodox.

8. Pharmacovigilance topics often concern predominantly qualitative information. For precise quantitative information (e.g. frequency), additional studies are often needed.

9. Signal detection speed is directly dependent on the size of the monitored population of drug users and therefore on the proportion of doctors contributing to the reporting system. Under-reporting delays the detection of rare adverse effects. In addition, the capacity of spontaneous reporting to provide clues with regard to the frequency of adverse effects (important for regulatory decision making) also depends on the proportion of reporting doctors.

10. The integration of national and international pharmacovigilance may require further development.

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Appendix 1

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